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Dear Dr. Thayer:

I am a neuroendocrinologist, nutritionist, professor at the University of Arkansas for Medical Sciences, and the Director of the Arkansas Children's Nutrition Center (one of the six centers in the National Human Nutrition Research Centers Program). For the past 15 years, a major part of my professional career has focused on research of various aspects of soy foods, soy protein, soy phytochemicals and soy formula.

I am also the Principal Investigator on what is, to my knowledge, the largest and most comprehensive prospective and longitudinal clinical study of children (birth to age 6 years) who are/were fed soy formula (the *Beginnings* study). The *Beginnings* study was initiated because there had been no head to head comparison of breast feeding with milk or soy formula. We are addressing many novel and important issues, such as the effects of infant feeding on; growth, development, body composition, metabolism, endocrine status, reproductive organ sizes, brain development, cognitive function, learning abilities, attention, language acquisition, and behavioral development. We are also studying psychological behavior of parents and the reasons why parents select infant feeding methods. Consequently, our research group has as much or more experience with infants fed soy formula than any other institution or individual.

In parallel, we have studied a variety of animal models in which whole soy foods, soy proteins, extracts of the soybean or purified soybean phytochemicals have been incorporated into their diet and fed throughout life or during specific "developmental windows". We use these models to address the mechanisms by which soy foods affect metabolism, development and endocrine status. Our experiences dealing with children, as well as developing and adult animals have taught us a great deal. I welcome this opportunity to share with you and the expert panel on soy formula some of the insights we have gained.

First, soy formula is a complex mixture of dietary components carefully selected and regulated by the FDA to provide nutrient requirements for human growth and development. As stated in the recent 2008 infant feeding report by the American Academy of Pediatrics (Pediatrics; 121:1062-8), growth and development of children fed soy formula equals that of breast-fed or milk formula-fed children. The AAP recommends soy formula under circumstances where breast feeding and milk formula feeding is inappropriate.

The study of developmental and health effects of soy formula needs careful attention to specific components. First and foremost, rather than taking a reductionist approach by studying a single component of soy formula, such as the aglycone genistein, the developmental and health effects of the complete soy formula should be determined. As all toxicologists recognize, the effects of one compound can be greatly affected by the presence or absence of other compounds. Therefore, the study of a single compound out of the context of how it is normally consumed or used can lead to results and conclusions that do not apply to the parent product. In fact, in many cases studying the effects of a single dietary compound isolated from the parent food can result in reaching opposite conclusions. Thus, one important and common limitation in published research aimed at investigating the health effects of soy formula is the exclusive emphasis on isolated soy components, mainly isoflavones and in particular genistein. Furthermore, in most instances the isoflavone aglycone form (genistein) is studied rather than the glycosylated form, genistin, the form that exists in soy formula. Less than 2% of the total genistein/genistin content is present as genistein in soy formula. We have shown that when consumed orally aglycones are metabolically handled in a different manner than the aglycone equivalents resulting in pharmacologic and pharmacokinetic differences that produce unique target tissue concentrations, molecular forms and bioactivities. Thus, use of aglycones to mimic soy formula translates into spurious health results.

Our experience in working with children, monkeys, pigs, and rodents, shows that results from studies that do not involve whole soy formula do not model the human condition (i.e., of infants fed soy formula). This is not to say that the study of phytochemical mixtures or even individual soy components has no relevance to children fed soy formula. However, it is only relevant when addressing mechanisms of specific biological effects of soy formula identified to occur in infants who were fed soy formula or in appropriate animal models where soy formula is fed. Otherwise, while the results of a carefully conducted experiment involving feeding or injections of a purified soy photochemical (i.e., genistein) to a baby mouse or rat can be interesting, our experience is that results from such studies do not apply to human infants fed soy formula. Furthermore, human infants are never exposed to those conditions.

This latter point also illustrates another important feature of research involving the health effects of soy formula. The animal models employed in most studies purported to relate to soy formula do not model the human infant and are therefore inappropriate. Rodents have limited use (utility) in identifying the effects of soy formula because it is very difficult to "bottle feed" a newborn rat or mouse. In fact, **there have been no published studies of newborn rodents fed soy formula**. The closest model for feeding rodent infants a liquid formula would be the "pup-in-the-cup model", which is an intragastric feeding model which has never been used for such studies.

Injecting isoflavones into pregnant or baby rodents simply does not model feeding soy formula to human infants, either on the basis of: diet composition; entry of bioactive compounds into the body; concentrations of circulating and excreted metabolites; using purified compounds rather than whole diet; or the stage of life in which such challenges are given. Such experiments would only model human infants of mothers who were

injected with isoflavones during pregnancy or breast-fed babies injected with pure isoflavones during the immediate post-natal period. **In addition, it should be pointed out that studies in which isoflavones are injected or fed as part of a diet to ***weanling*** rodents also do not model any human condition, yet the CERHR Panel has considered results from such studies as having "utility".** Thus, the published studies of rodents have not modeled human infants fed soy formula.

Another limitation to the use of rodents for the study of soy formula is that rodents have a completely different isoflavone metabolic profile than humans. For example, none of the 400 infants we have studied had detectable levels of the metabolite of daidzein, known as equol, which is one of the most potent estrogenic isoflavones resulting from soy intake. In contrast, in response to mixed isoflavones as exist in soy formula the predominant circulating isoflavonoid in rodents is equol.

An underlying theme of the research included in the NIEHS and the CERHR report is the potential estrogenic effects of isoflavones as demonstrated in rodent and *in vitro* studies. There is, however, a large leap between the results of these studies and the potential for estrogenic effects in infants fed soy formula. As mentioned above, the rodent does not model the human infant metabolism (gut bacteria, metabolism, etc.), there have been no studies of infant formula in rodents, and nearly all *in vivo* studies have been conducted with purified isoflavones and most have been administered by injection. The main point in these studies almost always related to estrogenic effects. However, we have very clearly demonstrated a unique gene expression profile in rats fed a diet made with 100% of the protein as soy protein isolate (SPI, the same protein used to produce soy formula) as compared to rats treated with estradiol, even though rats produce the most estrogenic isoflavone (equol); whereas, human infants do not. This is an extremely important point, because the bioactivities of estrogens occur mainly by turning on and turning off genes.

Our studies in rodents, pigs and children demonstrate no estrogenic effects of dietary soy protein (SPI) or soy formula during development. In fact, our study of very well-characterized infants (breast-fed, milk formula-fed or soy-fed) found no estrogenic differences unique to soy formula in the size of estrogen sensitive reproductive organs at the ages 3 and 6 months when peak blood isoflavone concentrations occur (Gilchrist et al; J Pediatr 2009). We have carefully studied brain and behavioral development, body composition and all aspects of child growth using standardized and accepted pediatric procedures. All of these measures were within the normal ranges of standardized testing and soy-fed infants consistently match either breast-fed or milk formula-fed infants and children in all aspects. We have absolutely no data or reason to believe that developmental, reproductive or any other health problems exist or will develop. Interestingly, infants fed milk formula had significantly larger ovaries than breast-fed infants. Does that mean that milk formula should not be fed to infants?

I want to make it clear that for several reasons I still encourage more research on the topic of soy formula. Research is needed because an international controversy exists about the health effects of soy formula and yet it remains an important option for infants with galactosemia, hereditary lactase deficiency, secondary lactose intolerance and for

infants who are part of a vegetarian (vegan) home. Furthermore, soy formula has been and continues to be used at inexplicably high rates in millions of American infants who do not have the above mentioned conditions. **However, I object to** clinical research based on data from studies that do not model the human condition (i.e., very poor rationale and data with no demonstrated human significance). The rationale and preliminary data must be solid and sufficient to warrant clinical investigation. There simply are no strong and convincing data (human or otherwise) demonstrating potential adverse effects of soy formula on infant or child development or reproductive function. Thus, any NIH-related report suggesting that such danger exists without appropriate supportive data unnecessarily produces anxiety and guilt in parents who have fed their infants soy formula.

Finally, I want to make it clear that the soy industry has not provided any financial support for my research nor do I have any financial ties to the soy industry. I have served on the science advisory board of the Soy Nutrition Institute, just like I have served on other industry and university boards and NIH committees. Serving on such boards and committees is an important and obvious scientific and university obligation and is a common and expected duty as director of a nutrition center.

Sincerely,

Redacted

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Director
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